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Lawrence Livermore National Security, LLC
LAWRENCE LIVERMORE NATIONAL LABORATORY
PO BOX 808, L-703
LIVERMORE, CA 94551-0808

EXAMINER	
BERTAGNA, ANGELA MARIE	

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Please find below and/or attached an Office communication concerning this application or proceeding.

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BEFORE THE BOARD OF PATENT APPEALS AND INTERFERENCES

Application Number: 10/727,779
Filing Date: December 03, 2003
Appellant(s): GARDNER ET AL.

Eddie Scott
For Appellant

EXAMINER'S ANSWER

This is in response to the appeal brief filed December 18, 2008 appealing from the Office action mailed September 26, 2008.

(1) Real Party in Interest

A statement identifying by name the real party in interest is contained in the brief.

(2) Related Appeals and Interferences

The examiner is not aware of any related appeals, interferences, or judicial proceedings which will directly affect or be directly affected by or have a bearing on the Board's decision in the pending appeal.

(3) Status of Claims

The statement of the status of claims contained in the brief is correct.

(4) Status of Amendments After Final

No amendment after final has been filed.

(5) Summary of Claimed Subject Matter

The summary of claimed subject matter contained in the brief is correct.

(6) Grounds of Rejection to be Reviewed on Appeal

The appellant's statement of the grounds of rejection to be reviewed on appeal is correct.

(7) Claims Appendix

The copy of the appealed claims contained in the Appendix to the brief is correct.

(8) Evidence Relied Upon

6,994,963	Murphy et al.	2-2006
US 2003/0087238	Evans et al	5-2003
WO 00/42560	Selifonov et al.	7-2000

(9) Grounds of Rejection

The following ground(s) of rejection are applicable to the appealed claims:

Priority

Applicant's claim for the benefit of a prior-filed application under 35 U.S.C. 119(e) or under 35 U.S.C. 120, 121, or 365(c) is acknowledged. Applicant has not complied with one or more conditions for receiving the benefit of an earlier filing date under 35 U.S.C. 119(e) and 120 as follows: The later-filed application must be an application for a patent for an invention which is also disclosed in the prior application (the parent or original non-provisional application or provisional application). The disclosure of the invention in the parent application and in the later-filed application must be sufficient to comply with the requirements of the first paragraph of 35 U.S.C. 112. See *Transco Products, Inc. v. Performance Contracting, Inc.*, 38 F.3d 551, 32 USPQ2d 1077 (Fed. Cir. 1994).

The disclosures of the prior-filed applications, Application No. 10/394,337 and Provisional Application No. 60/428,579, fail to provide adequate support or enablement in the manner provided by the first paragraph of 35 U.S.C. 112 for one or more claims of this application. Specifically, neither application provides support for the instant claims 16 and 17,

because the earlier-filed applications do not teach that the method is conducted using n-mers of a size n+1 or n+2 (claim 16) or that the method is conducted using oligos in multiple reading frames (claim 17). Therefore, since the earlier-filed applications do not provide adequate support for the instant claims 16 and 17, the filing date of the instant application (**December 3, 2003**) has been used for prior art purposes.

Claim Rejections - 35 USC § 112, 1st paragraph (New Matter)

The following is a quotation of the first paragraph of 35 U.S.C. 112:

> The specification shall contain a written description of the invention, and of the manner and process of making and using it, in such full, clear, concise, and exact terms as to enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the same and shall set forth the best mode contemplated by the inventor of carrying out his invention.

Claim 16 is rejected under 35 U.S.C. 112, first paragraph, as failing to comply with the written description requirement. The claim(s) contains subject matter which was not described in the specification in such a way as to reasonably convey to one skilled in the relevant art that the inventor(s), at the time the application was filed, had possession of the claimed invention. This is a new matter rejection.

As noted in MPEP 2163.06 I, "If new matter is added to the claims, the examiner should reject the claims under 35 U.S.C. 112, first paragraph - written description requirement. *In re Rasmussen*, 650 F.2d 1212, 211 USPQ 323 (CCPA 1981)."

Claim 16 is drawn to the method of claim 11, wherein the starting oligos of length n (n-mers), where n is an odd number, have a length of n+1 or n+2. Claim 16 as originally filed required the starting oligos to have a length n+1, n+2, etc. Therefore, the amendment to claim 16

broadens the scope of the claims by only requiring the starting oligos to have a length of n+1 **or** n+2 rather than lengths of n+1 **and** n+2, etc.

Applicant's response does not indicate where the amendment finds support in the original disclosure. The specification teaches in paragraphs 63 and 64 that the starting oligos have a length of n+1, n+2, *etc*, but does not provide support for a broader embodiment of the method wherein starting oligos having a length of n+1 or n+2, where n is an odd number, are used to practice the method of claim 11. Therefore, the method of amended claim 16 is not adequately supported by the original disclosure, and it has been rejected under 35 U.S.C. 112, first paragraph for incorporating new matter.

Claim Rejections - 35 USC § 102

The following is a quotation of the appropriate paragraphs of 35 U.S.C. 102 that form the basis for the rejections under this section made in this Office action:

> A person shall be entitled to a patent unless –
>
> (a) the invention was known or used by others in this country, or patented or described in a printed publication in this or a foreign country, before the invention thereof by the applicant for a patent.
>
> (e) the invention was described in (1) an application for patent, published under section 122(b), by another filed in the United States before the invention by the applicant for patent or (2) a patent granted on an application for patent by another filed in the United States before the invention by the applicant for patent, except that an international application filed under the treaty defined in section 351(a) shall have the effects for purposes of this subsection of an application filed in the United States only if the international application designated the United States and was published under Article 21(2) of such treaty in the English language.

Claim 11 is rejected under 35 U.S.C. 102(e) as being anticipated by Evans (US 2003/0087238 A1). This pre-grant publication was filed August 2, 2001.

Regarding claim 11, Evans discloses a method of producing a DNA molecule of 1-10 kb of user-defined sequence (paragraph 53 teaches production of a 5 kb sequence) comprising:

(a) virtually pre-selecting a multiplicity of DNA segments that will comprise a user-defined DNA molecule by using computational techniques to virtually break the DNA molecule into fragments of defined size (see Figure 3 and paragraphs 58, 82, and 189-195)

(b) providing fragments *in vitro* of length n (n-mers) of defined size that correspond to the virtual fragments (paragraphs 58, 82, and 195)

(c) arraying fragments *in vitro* by arraying the n-mers into groups (see Figure 3 and paragraphs 58, 82, and 195)

(d) separating the n-mers temporally *in vitro* (see paragraphs 58 and 62, where Evans teaches sequential addition of the segments)

(e) assembling the groups *in vitro* into double-stranded DNA molecules of predetermined base-pairs using parallel synthesis, DNA shuffling, and DNA polymerase to produce the DNA molecule of user-defined sequence (paragraphs 58 and 68 teach assembly using a polymerase; paragraphs 38, 93-98, and 195-199 teach assembly by PCR, which inherently comprises parallel synthesis and shuffling using a DNA polymerase)

wherein the step of separating the DNA sequence segments occurs temporally (see paragraphs 58 and 62) and the step of assembling the groups into double-stranded DNA molecules of pre-determined base pairs is accomplished by adding the DNA sequence segments gradually, in sequence order (paragraphs 58 and 62).

Further regarding claim 11, Evans teaches that the sequential addition minimizes errors (paragraph 66) and that computational techniques may be use to optimize (*i.e.* minimize errors) in the entire method (paragraph 178). Evans further teaches that the resulting polynucleotide is 5

kb (paragraph 53), which anticipates the claimed size range of 1-10 kb. Evans also teaches that the oligos used in the method have a length n, which is an odd number (paragraphs 58 & 82).

Claims 16 and 17 are rejected under 35 U.S.C. 102(a) and 102(e) as being anticipated by Evans (2003/0087238 A1).

As noted above, claims 16 and 17 have not been granted benefit of the earlier filing date of the previously filed provisional and non-provisional applications, but rather the instant application filing date of December 3, 2003. As a result, Evans qualifies as prior art under 35 U.S.C. 102(a) **and** 102(e).

Regarding claim 16, Evans teaches that the oligonucleotides may be different lengths (paragraph 53). Evans further teaches examples of oligonucleotides with lengths of 15 (n), 16 (n+1), or 17 (n+2) (see paragraph 53).

Regarding claim 17, Evans teaches that the multiplicity of DNA fragments comprises oligos in multiple reading frames. Specifically, Evans teaches variation of the oligo length and overlap between the fragments (paragraphs 53 and 54). These DNA fragments inherently comprise multiple reading frames.

Claim Rejections - 35 USC § 103

The following is a quotation of 35 U.S.C. 103(a) which forms the basis for all obviousness rejections set forth in this Office action:

> (a) A patent may not be obtained though the invention is not identically disclosed or described as set forth in section 102 of this title, if the differences between the subject matter sought to be patented and the prior art are such that the subject matter as a whole would have been obvious at the time the invention was made to a person having ordinary skill in the art to which said subject matter pertains. Patentability shall not be negatived by the manner in which the invention was made.

This application currently names joint inventors. In considering patentability of the claims under 35 U.S.C. 103(a), the examiner presumes that the subject matter of the various claims was commonly owned at the time any inventions covered therein were made absent any evidence to the contrary. Applicant is advised of the obligation under 37 CFR 1.56 to point out the inventor and invention dates of each claim that was not commonly owned at the time a later invention was made in order for the examiner to consider the applicability of 35 U.S.C. 103(c) and potential 35 U.S.C. 102(e), (f) or (g) prior art under 35 U.S.C. 103(a).

Claims 11 and 17 are rejected under 35 U.S.C. 103(a) as being unpatentable over Selifonov et al. (WO 00/42560) in view of Evans (US 2003/0087238 A1).

Selifonov discloses a method of making polynucleotides having user-defined characteristics (see for a general description, pages 3-6 "Summary of Invention" and also page 9, lines 23-31).

Regarding claim 11, Selifonov discloses a method of producing a DNA molecule of user-defined sequence comprising:

(a) virtually preselecting a multiplicity of DNA segments that will comprise a user-defined DNA molecule by using computational techniques to virtually break the DNA molecule into virtual fragments of length n (n-mers), where n is an odd number (page 14, lines 20-29 and page 21, lines 12-22 teach using computational methods to virtually break the DNA molecule into virtual fragments; page 6, lines 8-10 teach using n-mers where n is an odd number)

(b) providing fragments of length n (n-mers) of defined size, where n is an odd number, that correspond to the virtual fragments (page 9, lines 23-31 and page 21, lines 12-30 teach

providing fragments *in vitro* that correspond to the virtual fragments generated in step (a) above; page 6, lines 8-10 teaches using n-mers where n is an odd number in the synthesis method)

(c) arraying the fragments of defined size into groups (page 14, lines 27-30, where Selifonov teaches that the fragments may be left with the parental strands or transferred to a new population. Selifonov also teaches formation of new populations; see also page 21, lines 14-15 and lines 23-30, where sets are combined)

(d) separating the DNA sequence segments temporally (page 22, lines 4-19, where Selifonov teaches variation of the composition of fragments in the recombination reaction and/or performing multiple recombination reactions. This is a temporal separation of the DNA segments)

(e) assembling the groups into double-stranded DNA molecules of predetermined base-pairs using parallel synthesis, DNA shuffling, and DNA polymerase to produce the DNA molecule of user-defined sequence (page 21, line 23 – page 22, line 13).

See also Figures 4A-D for a flow-chart depiction of the method of Selifonov.

Further regarding claim 11, Selifonov teaches that the assembled polynucleotide of user-defined sequence is 1.6 kb (page 70), a value within the claimed range of 1-10 kb. Selifonov also teaches computational modeling in an effort to minimize reassembly errors (see for example, page 10, lines 26-33). However, Selifonov does not explicitly teach sequential addition of DNA segments in the reassembly process.

Regarding claim 17, Selifonov teaches that the multiplicity of DNA fragments comprises oligos in multiple reading frames. Specifically, Selifonov teaches variation of the oligo length

and overlap between the fragments (page 33, lines 1-6). These DNA fragments inherently comprise multiple reading frames.

Evans teaches a method of synthesizing a user-defined nucleic acid sequence that anticipates the instant claims 11, 16, and 17, as discussed above.

Regarding claim 11, Evans teaches that addition of the oligonucleotides in a sequential order (optimized by computational modeling) minimizes reassembly errors (see paragraphs 58, 66, and 178). Specifically, Evans stated, "The sequential polynucleotide assembly methods of the invention further reduce the error rate observed with methods that require hybridization of pools of large numbers of oligonucleotides (paragraph 66)." Evans further stated, "The sequential polynucleotide assembly methods of the invention eliminate the need for purification and allow for systematic assembly of identical sized double-stranded or single-stranded oligonucleotides (paragraph 66)."

It would have been *prima facie* obvious to one of ordinary skill in the art at the time the invention was made to utilize the *in silico*-optimized sequential addition of DNA fragments taught by Evans in the nucleic acid synthesis method of Selifonov. Evans expressly taught the advantages of sequential addition of oligonucleotide segments in sequence order, namely: (1) a reduction in the assembly error rate, (2) elimination of the need for an extra purification step and (3) parallel synthesis of identical-sized nucleic acids (see paragraph 66 and above). An ordinary artisan would have been motivated by these teachings of Evans to sequentially add the fragments to the reassembly reaction in sequence order in order to improve the accuracy of the reassembly reaction, eliminate the need for further purification (thereby improving the speed and efficiency of the process), and obtain the ability to synthesize in parallel multiple, identically-sized nucleic

acids. Thus, the methods of claims 11 and 17 are *prima facie* obvious over Selifonov in view of Evans.

9. Claim 16 is rejected under 35 U.S.C. 103(a) as being unpatentable over Selifonov et al. (WO 00/42560) in view of Evans (US 2003/0087238 A1) and further in view of Murphy et al. (US 6,994,963).

The combined teachings of Selifonov and Evans result in the methods of claims 11 and 17, as discussed above.

Selifonov teaches variation of DNA segment lengths and the use of a set of DNA segments comprising fragments of different lengths (see page 6, lines 8-10 and page 33, lines 1-6). However, Selifonov does not explicitly teach fragments of n+1 or n+2.

Murphy teaches a method of nucleic acid recombination. Briefly, the method of Murphy comprises primer extension and cleavage to create an "extension ladder" (column 4, lines 9-16) followed by recombinatorial synthesis to produce a mutagenized or chimeric nucleic acid (column 6, lines 34-40).

Regarding claim 16, Murphy teaches that the "extension ladder" (a collection of DNA segments) may comprise sequences of different length, specifically, sequences different by one nucleotide increments (*i.e.* n, n+1 or n+2) (see column 6, lines 49-56). Regarding the differently sized sequences, Murphy stated, "Furthermore, the present invention may use a complete library of nucleic acid extension products that differ in length by a single base. As a result, recombinatorial mutagenesis results in recombined sequences with potential crossover points at every single nucleotide in a nucleic acid sequence (column 3, line 66 – column 4, line 4)."

It would have been *prima facie* obvious for one of ordinary skill in the art at the time of invention to utilize DNA fragments differing by one nucleotide in length (n, n+1, n+2, etc) in the recombination method resulting from the combined teachings of Selifonov and Evans, since Murphy expressly taught that such a fragment pool resulted in "recombined sequences with potential crossover points at every single nucleotide in a nucleic acid sequence (column 3, line 66 – column 4, line 4)." An ordinary practitioner of the method resulting from the combined teachings of Selifonov and Evans would have been motivated by the teachings of Murphy to utilize the above length-diverse fragment pool in order to maximize the diversity of the resulting recombined/reassembled sequences, thereby improving the method's ability to generate nucleic acids encoding proteins with improved functional properties. Thus, the method of claim 16 is *prima facie* obvious in view of the combined teachings of Selifonov, Evans, and Murphy.

(10) Response to Argument

Rejection #1 – Rejection of claim 16 under 35 U.S.C. 112, 1st paragraph (new matter)

Applicant argues that the limitation "starting oligos of length n+1 or n+2" finds support in the original specification and drawings, specifically in original claim 16, Figure 7, and paragraphs 9, 63, and 64 (see pages 13-14). Applicant further argues that there would be no question of support for the terms "starting oligos of length n+1" or "starting oligos of length n+2", and therefore, the limitation "starting oligos of length n+1 or n+2" does not constitute new matter (pages 14-15).

As an initial matter, it is noted that on page 13 of the appeal brief, Applicant indicates that drawing figure 4 is reproduced on the next page. This appears to be a typographical error, since drawing figure 7 is reproduced on the next page of the appeal brief.

Applicant's arguments were not persuasive, because as discussed above, the original disclosure does not provide adequate support for claim 16 as amended. Prior to amendment, claim 16 required the use of starting oligonucleotides (oligos) of length n, wherein n is an odd number, having a length of n+1, n+2, *etc*. This claim language required the use of a **mixture** of starting oligos having lengths of n+1, n+2, *etc*, where n is an odd number. For example, this claim language encompassed an embodiment wherein a mixture of 5-mers, 6-mers, and so on (*i.e.* oligonucleotides having lengths of 5, 6, 7, 8, *etc* nucleotides) are used as the starting oligos. The original disclosure provides support for the language "starting oligos of length n, wherein n is an odd number, of length n+1, n+2, *etc*" (see paragraphs 9, 63, and 64 of the specification, as noted by Applicant and in the previously made rejection reiterated above). However, amended claim 16 has a different scope compared to the previously presented version of the claim. Specifically, the recitation "starting oligos of length n+1 **or** n+2" changes the scope of the claim to require starting oligos of **only one** of the lengths (*i.e.* n+1 **or** n+2), whereas the previous version of the claim required starting oligos having a plurality of different lengths (*i.e.* n+1 **and** n+2, *etc*).

The original disclosure provides support for the use of starting oligos having a single length in Figures 2-3 and paragraphs 18-19, 25-26, 33-34, 40, 46-51, and 58. However, in these embodiments of the invention, the starting oligos all have a length of n, rather than n+1 or n+2 as required by amended claim 16. Also, the embodiment described in Figure 7 and paragraph 68,

where tetramers were mixed with pentamers, does not provide adequate support for amended claim 16, because in this embodiment n = 4, which is not an odd number as required by amended claim 16. The original disclosure does not teach that starting oligos of a single length, specifically n+1 or n+2, where n is an odd number, can be used to practice the method of clam 11. Thus, the original disclosure does not provide adequate support for claim 16 as amended.

Finally, it is noted that, in contrast to Applicant's arguments at pages 14-15, amendment of claim 16 to recite either the limitation "oligos of length n+1" or the limitation "oligos of length n+2" would also raise a new matter issue for the same reasons set forth above. Either of these limitations would also present a situation in which the claims are drawn to the use of only starting oligos of a single length (*i.e.* n+1 **or** n+2), whereas the original disclosure only provides support for the use of starting oligos of a mixture of lengths (*i.e.* n+1, n+2, *etc*), when n is an odd number. For these reasons, Applicant's arguments were not persuasive, and claim 16 is considered to incorporate new matter.

Rejection #2 – Rejection of claim 11 under 35 U.S.C. 102(e) as being anticipated by Evans

Applicant argues that the Evans reference does not teach the following limitations in claim 11: (1) assembling the groups in vitro into double-stranded DNA molecules of predetermined base pairs using parallel synthesis, DNA shuffling, and DNA polymerase, (2) adding the DNA sequence segments gradually, in sequence order, (3) adding the DNA segments in an order computationally predicted to minimize errors, and (4) that the oligos used in the method have a length n, which is an odd number (see pages 17-18). Applicant also reproduces

the recited process steps of claim 11 and argues that Evans does not teach the recited combination of elements (see pages 18-19).

As an initial matter, it is noted that the appeal brief appears to contain a typographical error on page 18, where Applicant states that the rejection of claim 11 under 35 U.S.C. 102 as being anticipated by Evans was made under 35 U.S.C. 102(b). The rejection was made under 35 U.S.C. 102(e).

Applicant's arguments regarding the teachings of Evans were not persuasive, because no specific evidence or arguments relating to the alleged deficiencies in the reference have been presented. The arguments presented at pages 17-19 are general in nature asserting that the Evans reference fails to teach the claimed method, but they offer no specific reasons as to why the reference is deficient. As discussed previously and reiterated above, Evans teaches all of the elements of the instant claim 11. Evans teaches *in vitro* assembly using a polymerase at paragraphs 58 & 68. Evans also teaches *in vitro* assembly by PCR, which inherently comprises parallel synthesis and shuffling using a DNA polymerase, at paragraphs 38, 93-98, and 195-199. Evans teaches that the *in vitro* assembly step is conducted by adding the sequence segments gradually in sequence order at paragraphs 58 and 62, for example. Evans further teaches temporal separation of the DNA sequence segments at paragraphs 58 and 62. Evans also teaches that the sequential addition minimizes errors (paragraph 66) and that computational techniques may be use to optimize (*i.e.* minimize errors) in the entire method (paragraph 178). Evans also teaches that the oligos used in the method have a length n, which is an odd number, and the use of oligos having a length of n+1 or n+2 (paragraphs 53, 58, & 82). The previously made rejection has also been reproduced below.

Regarding claim 11, Evans discloses a method of producing a DNA molecule of 1-10 kb of user-defined sequence (paragraph 53 teaches production of a 5 kb sequence) comprising:

(a) virtually pre-selecting a multiplicity of DNA segments that will comprise a user-defined DNA molecule by using computational techniques to virtually break the DNA molecule into fragments of defined size (see Figure 3 and paragraphs 58, 82, and 189-195)

(b) providing fragments *in vitro* of length n (n-mers) of defined size that correspond to the virtual fragments (paragraphs 58, 82, and 195)

(c) arraying fragments *in vitro* by arraying the n-mers into groups (see Figure 3 and paragraphs 58, 82, and 195)

(d) separating the n-mers temporally *in vitro* (see paragraphs 58 and 62, where Evans teaches sequential addition of the segments)

(e) assembling the groups *in vitro* into double-stranded DNA molecules of predetermined base-pairs using parallel synthesis, DNA shuffling, and DNA polymerase to produce the DNA molecule of user-defined sequence (paragraphs 58 and 68 teach assembly using a polymerase; paragraphs 38, 93-98, and 195-199 teach assembly by PCR, which inherently comprises parallel synthesis and shuffling using a DNA polymerase)

wherein the step of separating the DNA sequence segments occurs temporally (see paragraphs 58 and 62) and the step of assembling the groups into double-stranded DNA molecules of pre-determined base pairs is accomplished by adding the DNA sequence segments gradually, in sequence order (paragraphs 58 and 62).

Further regarding claim 11, Evans teaches that the sequential addition minimizes errors (paragraph 66) and that computational techniques may be use to optimize (*i.e.* minimize errors) in the entire method (paragraph 178). Evans further teaches that the resulting polynucleotide is 5 kb (paragraph 53), which anticipates the claimed size range of 1-10 kb. Evans also teaches that the oligos used in the method have a length n, which is an odd number (paragraphs 58 & 82).

For these reasons Applicant's arguments were not persuasive, and Evans is considered to anticipate claim 11.

Rejection #3 – Rejection of claims 16 and 17 under 35 U.S.C. 102(a) and 35 U.S.C. 102(e) as being anticipated by Evans

Applicant first argues that the Evans reference fails to teach the following limitations of claim 11, from which claims 16 and 17 depend: (1) assembling the groups in vitro into double-stranded DNA molecules of predetermined base pairs using parallel synthesis, DNA shuffling, and DNA polymerase, (2) adding the DNA sequence segments gradually, in sequence order, (3)

adding the DNA segments in an order computationally predicted to minimize errors, and (4) that the oligos used in the method have a length n, which is an odd number, and therefore, the reference cannot anticipate claims 16 and 17 (pages 19-20).

Applicant also argues that Evans fails to teach the following limitations recited in claims 16 and 17: (1) that the starting oligos used in the method have lengths of n+1 or n+2 (claim 16), and (2) the oligos used in the method comprise oligos in multiple reading frames (claim 17) (see page 20).

Applicant also reproduces claims 16 and 17 including the limitations recited in independent claim 11 and asserts that Evans does not teach the combination of elements recited in claims 16 and 17 (see pages 20-22).

Applicant's arguments regarding the teachings of Evans were not persuasive, because no specific evidence or arguments relating to the alleged deficiencies in the reference have been presented. The arguments presented at pages 19-22 are general in nature asserting that the Evans reference fails to teach the claimed methods, but they offer no specific reasons as to why the reference is deficient. As discussed previously and reiterated above, Evans teaches all of the elements of the instant claim 11, 16, and 17. The teachings of Evans with respect to claim 11 have been discussed above. Regarding claims 16 and 17, Evans teaches that the oligos used in the method have a length n, which is an odd number, and also the use of oligos having a length of n+1 or n+2 (paragraphs 53, 58, & 82). Evans teaches variation of the oligo length and overlap between the fragments at paragraphs 53 and 54, which inherently results in the use of oligos that comprise multiple reading frames.

For these reasons Applicant's arguments were not persuasive, and Evans is considered to anticipate claims 16 and 17.

Rejection #4 – Rejection of claims 11 and 17 under 35 U.S.C. 103(a) as being unpatentable over Selifonov in view of Evans

Applicant first argues that the cited references do not teach or suggest all of the limitations of the rejected claims. Applicant argues that neither reference teaches the following limitations of claim 11: (1) assembling the groups in vitro into double-stranded DNA molecules of predetermined base pairs using parallel synthesis, DNA shuffling, and DNA polymerase, (2) adding the DNA sequence segments gradually, in sequence order, (3) adding the DNA segments in an order computationally predicted to minimize errors, and (4) that the oligos used in the method have a length n, which is an odd number (see pages 25-27). Applicant also argues that neither reference teaches the limitations recited in claim 17 (see pages 25-27).

Applicant's first argument was not persuasive, because it is general in nature and fails to identify specific reasons why the combined teachings of the cited reference do not result in all of the limitations of the rejected claims. As discussed previously and above, the combined teachings of Selifonov and Evans teach or suggest all of the limitations of claims 11 and 17. Each of the limitations recited in the rejected claims is addressed by Selifonov and Evans in the rejection outlined above and identified by Figure, page and line number, or paragraph number. The teachings of Selifonov and Evans with respect to claims 11 and 17 are reproduced below:

Selifonov discloses a method of making polynucleotides having user-defined characteristics (see for a general description, pages 3-6 "Summary of Invention" and also page 9, lines 23-31).

Regarding claim 11, Selifonov discloses a method of producing a DNA molecule of user-defined sequence comprising:

(a) virtually preselecting a multiplicity of DNA segments that will comprise a user-defined DNA molecule by using computational techniques to virtually break the DNA molecule into virtual fragments of length n (n-mers), where n is an odd number (page 14, lines 20-29 and page 21, lines 12-22 teach using computational methods to virtually break the DNA molecule into virtual fragments; page 6, lines 8-10 teach using n-mers where n is an odd number)

(b) providing fragments of length n (n-mers) of defined size, where n is an odd number, that correspond to the virtual fragments (page 9, lines 23-31 and page 21, lines 12-30 teach providing fragments *in vitro* that correspond to the virtual fragments generated in step (a) above; page 6, lines 8-10 teaches using n-mers where n is an odd number in the synthesis method)

(c) arraying the fragments of defined size into groups (page 14, lines 27-30, where Selifonov teaches that the fragments may be left with the parental strands or transferred to a new population. Selifonov also teaches formation of new populations; see also page 21, lines 14-15 and lines 23-30, where sets are combined)

(d) separating the DNA sequence segments temporally (page 22, lines 4-19, where Selifonov teaches variation of the composition of fragments in the recombination reaction and/or performing multiple recombination reactions. This is a temporal separation of the DNA segments)

(e) assembling the groups into double-stranded DNA molecules of predetermined base-pairs using parallel synthesis, DNA shuffling, and DNA polymerase to produce the DNA molecule of user-defined sequence (page 21, line 23 – page 22, line 13).

See also Figures 4A-D for a flow-chart depiction of the method of Selifonov.

Further regarding claim 11, Selifonov teaches that the assembled polynucleotide of user-defined sequence is 1.6 kb (page 70), a value within the claimed range of 1-10 kb. Selifonov also teaches computational modeling in an effort to minimize reassembly errors (see for example, page 10, lines 26-33). However, Selifonov does not explicitly teach sequential addition of DNA segments in the reassembly process.

Regarding claim 17, Selifonov teaches that the multiplicity of DNA fragments comprises oligos in multiple reading frames. Specifically, Selifonov teaches variation of the oligo length and overlap between the fragments (page 33, lines 1-6). These DNA fragments inherently comprise multiple reading frames.

Evans teaches a method of synthesizing a user-defined nucleic acid sequence that anticipates the instant claims 11, 16, and 17, as discussed above.

Regarding claim 11, Evans teaches that addition of the oligonucleotides in a sequential order (optimized by computational modeling) minimizes reassembly errors (see paragraphs 58, 66, and 178). Specifically, Evans stated, "The sequential polynucleotide assembly methods of the invention further reduce the error rate observed with methods that require hybridization of pools of large numbers of oligonucleotides (paragraph 66)." Evans further stated, "The sequential polynucleotide assembly methods of the invention eliminate the need for purification

and allow for systematic assembly of identical sized double-stranded or single-stranded oligonucleotides (paragraph 66)."

Applicant also argues that the rejection fails to provide a reason for combining the teachings of the cited references (page 28).

This argument was not persuasive, because the rejection has provided a detailed discussion of the reasons an ordinary artisan would have been motivated to combine the teachings of the Selifonov and Evans references. Specifically, as discussed above, an ordinary artisan would have been motivated to utilize the *in silico*-optimized sequential addition of DNA fragments taught by Evans in the nucleic acid synthesis method of Selifonov, since Evans expressly taught that sequential addition of oligonucleotide segments in sequence order resulted in the following advantages: (1) a reduction in the assembly error rate, (2) elimination of the need for an extra purification step and (3) parallel synthesis of identical-sized nucleic acids (see paragraph 66). An ordinary practitioner of the nucleic acid synthesis method taught by Selifonov would have been motivated by the above teachings of Evans to sequentially add the fragments to the reassembly reaction in sequence order in order to improve the accuracy of the reassembly reaction, eliminate the need for further purification (thereby improving the speed and efficiency of the process), and obtain the ability to synthesize in parallel multiple, identically-sized nucleic acids.

For these reasons Applicant's arguments were not persuasive, and the combined teachings of Selifonov and Evans are considered to render obvious the methods of claims 11 and 17.

Rejection #5 – Rejection of claim 16 under 35 U.S.C. 103(a) as being unpatentable over Selifonov in view of Evans and further in view of Murphy

Applicant first argues that the combined teachings of Selifonov, Evans and Murphy fail to teach or suggest all of the limitations of the rejected claims. Applicant argues that none of the cited references teaches the following limitations of claim 11: (1) assembling the groups in vitro into double-stranded DNA molecules of predetermined base pairs using parallel synthesis, DNA shuffling, and DNA polymerase, (2) adding the DNA sequence segments gradually, in sequence order, (3) adding the DNA segments in an order computationally predicted to minimize errors, and (4) that the oligos used in the method have a length n, which is an odd number (see pages 30-32). Applicant also argues that neither reference teaches the limitations recited in claim 16 (see pages 30-32).

Applicant's first arguments were not persuasive, because they are general in nature and fail to identify specific reasons why the combined teachings of the cited references do not result in all of the limitations of the rejected claim. As discussed previously and above, the combined teachings of the Selifonov and Evans references teach or suggest all of the limitations of claims 11 and 17, and the Selifonov, Evans, and Murphy references teach or suggest all of the limitations of claim 16. Each of the limitations recited in the rejected claims is addressed by Selifonov, Evans, and Murphy in the rejection outlined above and identified by Figure, page and line number, paragraph number, or column and line number. The teachings of Selifonov and Evans with respect to claims 11 and 17 have been discussed above. The teachings of Selifonov and Murphy with respect to claim 16 have been reproduced below.

Selifonov teaches variation of DNA segment lengths and the use of a set of DNA segments comprising fragments of different lengths (see page 6, lines 8-10 and page 33, lines 1-6). However, Selifonov does not explicitly teach fragments of n+1 or n+2.

Murphy teaches a method of nucleic acid recombination. Briefly, the method of Murphy comprises primer extension and cleavage to create an "extension ladder" (column 4, lines 9-16) followed by recombinatorial synthesis to produce a mutagenized or chimeric nucleic acid (column 6, lines 34-40).

Regarding claim 16, Murphy teaches that the "extension ladder" (a collection of DNA segments) may comprise sequences of different length, specifically, sequences different by one nucleotide increments (*i.e.* n, n+1 or n+2) (see column 6, lines 49-56). Regarding the differently sized sequences, Murphy stated, "Furthermore, the present invention may use a complete library of nucleic acid extension products that differ in length by a single base. As a result, recombinatorial mutagenesis results in recombined sequences with potential crossover points at every single nucleotide in a nucleic acid sequence (column 3, line 66 – column 4, line 4)."

Applicant also argues that the rejection fails to provide a reason for combining the teachings of the cited references (page 33).

This argument was not persuasive, because the rejection has provided a detailed discussion of the reasons an ordinary artisan would have been motivated to combine the teachings of the Selifonov, Evans, and Murphy references. Specifically, as discussed previously and above, an ordinary artisan would have been motivated to utilize DNA fragments differing by one nucleotide in length (*i.e.* oligonucleotides of length n+1 or n+2, *etc*) in the recombination method resulting from the combined teachings of Selifonov and Evans, since Murphy expressly taught that such a fragment pool resulted in "recombined sequences with potential crossover points at every single nucleotide in a nucleic acid sequence (column 3, line 66 – column 4, line 4)." An ordinary practitioner of the method resulting from the combined teachings of Selifonov and Evans would have been motivated by these teachings of Murphy to utilize the above length-diverse fragment pool in order to maximize the diversity of the resulting

recombined/reassembled sequences, thereby improving the method's ability to generate nucleic acids encoding proteins with improved functional properties.

For these reasons Applicant's arguments were not persuasive, and the combined teachings of Selifonov, Evans, and Murphy are considered to render obvious claim 16.

(11) Related Proceeding(s) Appendix

No decision rendered by a court or the Board is identified by the examiner in the Related Appeals and Interferences section of this examiner's answer.

For the above reasons, it is believed that the rejections should be sustained.

Respectfully submitted,

/Angela Bertagna/
Examiner, Art Unit 1637

/GARY BENZION/
Supervisory Patent Examiner, Art Unit 1637

Conferees:

/Kenneth R Horlick/
Primary Examiner, Art Unit 1637

/GARY BENZION/
Supervisory Patent Examiner, Art Unit 1637

/Joseph T. Woitach/
Supervisory Patent Examiner, Art Unit 1633